Mudra *et al. J Cancer Metastasis Treat* 2019;5:27
DOI: 10.20517/2394-4722.2019.09

Journal of Cancer Metastasis and Treatment

Review

Open Access

Stereotactic radiosurgery in the era of novel systemic therapy for lung cancer brain metastases

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How to cite this article: Mudra S, Bhandari S, Tripathi P, Dunlap N, Kloecker G. Stereotactic radiosurgery in the era of novel systemic therapy for lung cancer brain metastases. *J Cancer Metastasis Treat* 2019;5:27. http://dx.doi.org/10.20517/2394-4722.2019.09

Received: 15 Jan 2019 **First Decision:** 6 Feb 2019 **Revised:** 13 Feb 2019 **Accepted:** 20 Feb 2019 **Published:** 3 Apr 2019

Science Editor: Lucyna Kepka **Copy Editor**: Cai-Hong Wang **Production Editor**: Huan-Liang Wu

Abstract

The emergence of novel systemic therapies has spurred a dramatic paradigm shift in lung cancer treatment. Research has revealed greater intracranial efficacy in targeted agents and immune checkpoint inhibitors (ICI) compared to conventional chemotherapy. Concurrently, advances in stereotactic radiosurgery (SRS) have contributed to the increased use of this highly localized, minimally-invasive treatment modality for local tumor control. In this era of precision medicine, the combination of these novel agents and SRS demands further prospective exploration - particularly as questions regarding their sequence of administration and the risk of neurotoxicity remain unanswered. Presently, although data are limited and largely retrospective, literature supports the concurrent administration of ICI and radiation, with no observed increases in immune-related adverse events or acute neurologic toxicities. In the case of patients with driver mutations, newer generations of tyrosine kinase inhibitors (TKI) display improved intracranial efficacy and are currently preferred alone upfront in patients with asymptomatic brain metastases (BM) due to lack of data. Evidence of combining TKI and SRS is limited with mixed results. In this review, we explore the evidence regarding the use of novel systemic agents and SRS for treatment of lung cancer BM. Clinical practice will continue to be refined as larger, prospective studies yield results.

Keywords: Lung cancer; stereotactic radiosurgery, brain metastasis, tyrosine kinase inhibitors, immunotherapy

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality[1]. Eighty-five percent of diagnoses represent non-small cell lung cancer (NSCLC)[2]; the remaining 10%-14% are diagnoses of small cell lung cancer. Brain metastases (BM) are diagnosed in approximately 10% of lung cancers at time of diagnosis[3] and approximately 40%-50% will be diagnosed with BM during the course of their disease[3,4]. BM in lung cancer are known to be associated with poor prognosis. Historically, standard treatment for BM from lung cancer involves neurosurgical resection[5], radiotherapy and/or chemotherapy[5,6].

Recent advances in NSCLC, including molecular analysis, matched targeted therapies and immunotherapy, has altered the standard of care. These novel approaches have shifted the paradigm in lung cancer[7] and improved median overall survival in lung cancer patients with BM[7,8]. Survival now ranges between 9-15 months and can be as high as 46 months in patients with favorable prognostic factors such as good performance status and epidermal growth factor receptor (EGFR) and/or anaplastic lymphoma kinase (ALK) positivity[9]. In addition, over the past decade, standard of care in radiotherapy for BM has increasingly favored SRS[10,11]. Precise delivery of high-dose radiation localized to the tumor results in higher local tumor control[10] and fewer side effects such as neurocognitive damage[11] compared to whole brain radiotherapy (WBRT).

The trifold advancement in targeted therapies, immunotherapy and SRS has revolutionized the treatment of BM in lung cancer. Employing these novel therapies, lung cancer patients are living longer, becoming more likely to develop brain metastases. Certainly, the use of these therapies - either individually or in combination - is anticipated for the treatment of lung cancer BM.

In this review, we discuss the current evidence regarding the use of SRS employed alone and in combination with novel therapies for treatment of lung cancer BM.

BRAIN METASTASIS IN LUNG CANCER LACKING A DRIVER MUTATION

SRS

SRS, typically delivered in a single fraction, serves as a key modality for delivering high-dose radiation to smaller target sites (usually < 3 cm)[12], sparing adjacent structures from exposure and mitigating the harmful effects of radiation[11].

For single BM, SRS has demonstrated efficacy and safety. Therefore, both surgical resection plus postoperative radiation and SRS alone are reasonable options and treatment should be individualized as comparative data is lacking[13]. Surgery plus postoperative radiation is preferred for a single, large and symptomatic BM to allow for decompression, lower morbidity and higher local control[13]. One small retrospective study found similar survival when comparing surgical resection *vs.* SRS for solitary BM[14]. However, more local recurrence was demonstrated in the surgery group[14].

For surgically-resected brain metastases, post-operative SRS (post-SRS) is the current standard of care. Some concerns with post-SRS include radiation necrosis and leptomeningeal disease (LMD) recurrence. The hypothesis behind LMD recurrence is the intra-operative seeding of viable tumor cells, which is supported by a study where post-SRS demonstrated higher rates of LMD compared to adjuvant WBRT[15]. A new approach, pre-operative SRS (pre-SRS), is being evaluated as a potential method to decrease radiation necrosis and LMD. Potential benefits of pre-SRS include: (1) better local tumor control through improved delineation when contouring an intact metastasis compared to an irregularly-shaped surgical cavity; (2) reduced risk of radiation necrosis, as there is no need to treat surrounding brain tissue and the majority of the treated BM will be resected; (3) reduced risk of LMD as a result of a potential sterilizing effect via the intraoperative seeding of treated tumor cells; and (4) the potential to treat more patients, as with post-

SRS some patients are lost to follow-up. A potential disadvantage includes reduced wound healing[15]. Asher *et al.*[16] evaluated pre-SRS in 47 patients, demonstrating its safety and efficacy with local control rates of 85.6% at 12 months. One retrospective study evaluating pre- and post-SRS cohorts of 180 BM patients (including approximately 40% with NSCLC) showed similar rates of local recurrence and overall survival. However, pre-SRS was associated with significantly reduced rates of radiation necrosis and LMD[17]. Clinical trials currently comparing pre-SRS and post-SRS in BM include NCT03741673 and NCT03750227.

SRS plays a major role in patients with multiple small BM (< 3 cm) or surgically inaccessible BM. Younger lung cancer patients of high Karnofsky performance status with limited BM and a low burden of extracranial disease may derive the most benefit from SRS[10,18]. Generally, SRS use has been limited to patients with few, small, easily radio-accessible BM[2]. Although a multi-center retrospective analysis demonstrated a survival advantage for patients treated with SRS possessing fewer than four BM (n = 189 for NSCLC) compared to WBRT (adjusted HR for NSCLC, 0.58; 95%CI: 0.38-0.87; P = 0.01)[19], Yamamoto and colleagues recently evaluated SRS alone in 1,194 patients with up to ten lesions (largest tumor < 10 mL in volume and < 3 cm in longest diameter; total cumulative volume ≤ 15 mL)[20]. Their group found no difference in overall survival (10.8 months) or treatment-related adverse events (9%) between patients with two to four tumors and patients with five to ten tumors[20]. These results suggest expanding SRS for the treatment of patients with up to ten BM[2,5]. Further data propose total BM volume as potentially more significant than the total number of BM[10].

Adverse effects of SRS

Overall, the adverse effects of SRS are consistent with known toxicities of intracranial irradiation. Both acute (developing over weeks to months) and late-onset (developing over months to years) toxicities may result. Certainly, the risk, severity and incidence of radiation-induced toxicities is highly dependent on the site, dose, fractionation and volume of tissue irradiated along with the patient's comorbidities[21]. Acute toxicities are uncommon and include nausea, headache, dizziness, seizure or new transient focal deficits[22]. Patients are usually treated with a short course of glucocorticoids.

The most common delayed adverse effect of SRS treatment to BM is radiation necrosis, occurring in approximately 5%-10% of patients[23]. However, this risk rapidly increases with increasing BM size and/or volume as well as with a history of radiation to same lesion[21,23-25]. A study suggests employing multifractionated SRS in three to five fractions rather than single fraction SRS as a means of decreasing the risk of radiation necrosis and improving local control[26]. The use of fractionated SRS also allows for the safe treatment of larger BM (> 3 cm)[26,27]. Data on long-term effects of SRS on neurocognition is limited but reassuring[25].

SRS in combination with immunotherapy

Immune checkpoint inhibitors (ICIs) have become a routine part of the treatment of advanced NSCLC lacking a driver mutation, administered with chemotherapy doublet or alone in patients with ≥ 50% expression of programmed cell death-ligand 1 (PD-L1)[8]. Most patients with advanced NSCLC and BM are eligible to receive ICIs - either alone or with chemotherapy.

Concerns to using ICIs to treat BM include: (1) pseudo-progression with the potential of symptom aggravation; and (2) steroid use for symptomatic BM which may reduce ICI activity, as demonstrated by a decreased objective brain response with the addition of steroids during ICI treatment in melanoma[28]. Present data on ICIs for BM from advanced NSCLC is limited. Most ICI clinical trials in NSCLC excluded patients with untreated or unstable BM, yet included stable and treated BM, comprising 6%-17% of included patients[29]. Overall, in the small subgroups of BM patients included in these trials, ICI appears safe[29]. However, outcomes were mixed as some trials demonstrated benefit over chemotherapy and others did not[29]. A rationale for positive response to ICIs includes the inflammatory microenvironment of BM, with

the presence of significant tumor-infiltrating lymphocytes (TILs). In a series of 116 BM specimens (including 61 from NSCLC BM), more than 50% of all specimens had dense TIL infiltration - also associated with improved survival[30].

Radiation therapy (RT) also induces an antitumor immune response by upregulating PD-L1 and inflammatory cytokines as well as facilitating T-cell infiltration[31]. Localized RT may induce an abscopal effect, which reflects the regression of non-irradiated metastatic lesions due to systemic anti-tumor response. The dose and fractionation of RT plays a role in its effects on the immune system. Schaue *et al*.[32] found that fractionated treatment with medium-sized radiation doses of 7.5 Gy per fraction yielded the best tumor control and anti-tumor immune responses. Dewan *et al*.[33] showed that 5 × 6 Gy and 3 × 8 Gy protocols of RT were more effective in inducing immune-mediated abscopal effects than a single ablative dose of 20 Gy when combined with an anti-CTLA-4 antibody. These preclinical data suggest a better systemic anti-tumor effect with hypo-fractionated (e.g., fractionated SRS) than conventional RT. Most data regarding the abscopal effect are from treating systemic disease; if the same impact occurs in the treatment of BM is uncertain. Although based on small studies, there is growing evidence in favor of an abscopal effect when treating BM[34].

RT alone is a poor inducer of immune-mediated local and abscopal responses; but, evidence suggests these responses are enhanced by combining radiation with ICI[31,35,36]. Although data regarding the combination of ICI and radiotherapy in BM due to NSCLC are limited and mostly retrospective, data indicate that combining ICI and radiation in BM is safe with similar adverse events[37,38] and support a concurrent administration of ICI with radiation over a sequential administration[38]. While most studies demonstrated similar adverse events with combination ICI-radiotherapy, the role of ICI in radiation necrosis remains controversial. One retrospective study with 61% NSCLC patients showed that the incidence of symptomatic radiation necrosis after stereotactic radiation was higher in patients who received ICI - especially those with melanoma[39]. Other retrospective studies including patients with NSCLC and BM did not report a higher indicence of radiation necrosis with combination ICI-radiotherapy[37,38,40].

Many questions regarding the combination of ICI and RT remain unanswered including the optimal timing, the impact of steroids and neurotoxicity. Questions such as these should be investigated through prospective trials. Current clinical trials evaluating the combination of ICI and radiation therapy in NSCLC BM include NCT02978404 (Nivolumab + SRS), NCT02858869 (Pembrolizumab + SRS) and NCT02696993 (Nivolumab + SRS/WBRT and Nivolumab + Ipilimumab + SRS/WBRT). These phase I and phase II trials include other malignancies and are expected to finish by 2020.

BRAIN METASTASIS IN LUNG CANCER WITH DRIVER MUTATIONS

In NSCLC, sensitizing EGFR mutations are found in 10% of Caucasians as well as up to 50% of Asians[41]. ALK-rearrangement is found in 2%-7%[42] and ROS proto-oncogene 1 (ROS1) occurs in 1%-2% of patients[43]. The incidence of BM is higher in patients with driver mutations. The rates of BM present at diagnosis is 24.2% and 23.8% in EGFR-mutated and ALK-rearranged lung cancers, respectively, and increasing to > 45% of patients at three years post-diagnosis[44]. ROS1-rearranged NSCLC also has a high incidence of BM (36%) and is the common first site of progression[45].

First- (erlotinib, gefinitib) and second-generation (afatinib) anti-EGFR TKI have demonstrated improved survival and brain response rates of over 50% in EGFR-mutated patients compared to EGFR wild-type patients[5]. The third-generation anti-EGFR TKI, osimertinib, demonstrated an even higher rate of intracranial response (91% *vs*. 68% in patients with measurable BM lesions), a lower rate of central nervous system (CNS) progression and longer progression-free survival when compared to first generation anti-EGFR TKI in the FLAURA trial[46,47]. Though first- and second-generation anti-EGFR TKI have activity in patients with BM, these agents have a much lower intracranial concentration as compared with osimertinib[5]. Given

the high intracranial activity of osimertinib, it is preferred as the initial therapy for patients presenting with asymptomatic BM in EGFR-mutated NSCLC. Osimertinib has not yet been evaluated with SRS, but it is reasonable to use SRS in the case of isolated intracranial progression and continue to use osimertinib. A clinical trial is open to evaluate osimertinib with or without SRS for EGFR-mutated NSCLC with BM (NCT03497767). The trial is expected to be completed in 2022.

If osimertinib is unavailable, first- or second-generation anti-EGFR TKI can be used in patients with asymptomatic BM, but not alone. Preclinical studies have shown a sensitizing effect of radiotherapy on EGFR expression and an enhanced radiation response through the inhibition of EGFR[48,49]. Although limited, clinical data is not yet reflective of preclinical data, but shows promise for future trials. A meta-analysis including 363 patients and another retrospective study of 351 patients with EGFR-mutated NSCLC (treated with first- and second-generation anti-EGFR TKI) suggested upfront intracranial radiation demonstrates better overall survival[50,51]. SRS followed by anti-EGFR TKI resulted in the longest overall survival, with WBRT followed by anti-EGFR TKI demonstrating intermediate overall survival and anti-EGFR TKI followed by SRS or WBRT at intracranial progression resulting in the shortest median overall survival[50,51]. Based on these data, for patients with asymptomatic BM started on a first- or second-generation anti-EGFR TKI, upfront SRS is appropriate - particularly given its better outcomes compared to delaying radiation. The concurrent use of anti-EGFR TKI with SRS or WBRT is more controversial, demonstrating mixed results. A phase III study found decreased overall survival with WBRT + SRS + erlobinib compared to WBRT + SRS[52]. Another retrospective study found similar survival in patients receiving a concurrent administration of radiation + anti-EGFR TKI *vs.* patients receiving radiation followed by anti-EGFR TKI[53]. At this point, due to the absence of data, we recommend stopping TKI administration during SRS treatment and resuming after completion.

ALK-directed TKIs have also demonstrated intracranial activity. In a retrospective analysis, the first-generation ALK inhibitor, crizotinib, showed an intracranial disease control rate of 56% in untreated BM and 62% in previously treated BM[54]. Despite this intracranial efficacy, approximately 20% of patients progressing on crizotinib developed BM[54]. Second-generation ALK-directed TKIs (ceritinib, alectinib, brigatinib) have better intracranial efficacy. Alectinib was compared to crizotinib in two phase III trials (J-ALEX and ALEX) and showed improved survival and superior CNS activity with an incidence rate of CNS progression at 12 months of 4.6% with alectinib compared to 32% with crizotinib in patients without BM at baseline[55-57]. Brigatinib is also superior to crizotinib in the frontline setting, as seen in the ALTA trial, with an intracranial response rate of 78% with brigatinib *vs.* 28% with crizotinib[58]. Crizotinib, ceritinib, alectinib and brigatinib are all approved as first-line therapies for ALK-positive advanced NSCLC. However, alectinib is preferred per National Comprehensive Cancer Network guidelines[8]. Alectinib alone is appropriate in asymptomatic BM.

In patients who progress on crizotinib, ceritinib, alectinib or brigatinib are all appropriate as they have not been directly compared in terms of BM efficacy. In a small case series, alectinib also showed intracranial response in ceritinib-resistant patients[59]. In the setting of alectinib-resistant disease, options include switching to lorlatinib, which has documented CNS activity in patients who have failed second-generation inhibitors[60] or local therapy (such as SRS) if only oligometastatic disease is present[61].

Crizotinib is the standard first-line treatment for patients with ROS1-rearranged NSCLC[8], but as previously discussed, it has poor intracranial activity. Other approved TKIs include ceritinib and lorlatinib that demonstrate better intracranial activity[62,63]. There are no data available on the combination of radiation therapy and TKI in ROS1-rearranged NSCLC.

In one study, patients with EGFR-mutated or ALK-rearranged NSCLC who had oligo-progression on erlotinib or crizotinib were considered for local ablative therapy to the sites of progression and continuation

of the TKI[64]. The TKI was stopped on the days of radiation and restarted with the same dose[64]. Twenty-five of 51 patients who progressed were deemed suitable for local therapy and most received stereotactic radiation[64]. Ten of the 25 patients had intracranial progression[64]. Post local ablative therapy, the median progression-free survival was six months[64]. Minimal grade three and four adverse events were seen[64]. Another study of ALK-rearranged NSCLC showed that combining stereotactic radiation with crizotinib is safe and can achieve durable control, although the study only included extracranial sites of progression[65]. A retrospective study showed prolonged overall survival (49.5 months) of NSCLC patients with BM when treated with ALK-directed TKI therapy and brain radiation[66]. In the ALEX trial, patients with previous radiation to BM had higher intracranial response rates (86% *vs.* 79%) compared with patients without prior radiotherapy[57]. In summary, data on the safety and outcome of combining radiation with ALK-directed TKIs is limited and favors SRS over WBRT.

An ongoing clinical trial is evaluating ALK inhibitors and other targeted therapies in combination with stereotactic brain treatment in patients with stage IV oncogene-driven (EGFR, ALK, or ROS1) NSCLC (NCT02314364).

CONCLUSION

The development of novel, targeted agents and immunotherapy has advanced the systemic treatment of lung cancer. These therapeutics demonstrate far greater intracranial efficacy than conventional chemotherapy - transformative for BM treatment. However, this paradigm shift in treatment warrants the careful consideration of systemic therapy as a frontline approach. While SRS remains an important aspect of the management of BM, its role combined with novel systemic therapies is largely unclear. Limited available evidence suggests combination is safe with favorable outcomes, but the sequence of administration remains uncertain. Many clinical trials are underway that aim to further address these questions. As the results of these studies emerge, clinicians will gain further evidence-based insight into the clinical management of patients with lung cancer BM.

DECLARATIONS

Authors' contributions

Made substantial contributions to the research, writing and editing of the manuscript: All authors

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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